Using blood markers for Alzheimer disease in clinical practice?

Sid E. O'Bryant, PhD

Correspondence & reprint requests to Dr. O'Bryant: Sid.o'bryant@unthsc.edu

Neurology® 2012;79:846–847

Until recently, the notion of having blood markers of Alzheimer disease (AD) available for clinical use was more likely to be seen in an episode of a TV medical drama or a science fiction movie than in a peer-reviewed scientific journal. The search for biomarkers suffered from serious obstacles, including, but not limited to, inadequate diagnostic accuracy, and an inability to replicate findings across samples between laboratories or even within individual laboratories. However, the serious scientific world took notice when, in 2007, Ray et al.[1] published a plasma-based screening tool that utilized advanced proteomic and bioinformatics methods to create a blood profile that was highly accurate in identifying persons with AD as well as those who were most likely to progress from mild cognitive impairment (MCI) to AD dementia. Enthusiasm diminished, however, when the findings did not replicate.[2] Despite that initial setback, there has been a surge in activity in the area of blood-based biomarkers for AD,[3–5] with more recent work achieving excellent diagnostic accuracy; furthermore, there has been cross-validation in independent cohorts and demonstration of comparable diagnostic accuracy, compared to that obtained from CSF biomarkers.[6] As a result of these advances, the clinical implementation of blood biomarkers has now become a regular topic of discussion not only within the research community, but also by clinicians, industry, and the lay public.

A key limitation to progress has been a proliferation of markers without cross-validation among projects. While the discovery of novel markers will continue to be of importance, it is imperative that currently identified putative markers be thoroughly investigated, lest the field be stuck forever in discovery science. In this issue of *Neurology*®, Hu et al.[7] take a very important step in that process by identifying plasma biomarkers that relate to MCI/AD status across 3 independent cohorts from the University of Pennsylvania (Penn), Washington University (WU), and the Alzheimer's Disease Neuroimaging Initiative (ADNI). A total of 17 markers were consistently related to MCI/AD status across the Penn and WU cohorts, which, when applied to the ADNI cohort, resulted in 6 notable markers across all 3 cohorts: apoE, B-type natriuretic peptide (BNP), cortisol, C-reactive protein (CRP), interleukin-3 (IL-3), and pancreatic polypeptide (PP). Many of these were also related to CSF markers of disease state, namely, Aβ42 levels and t-tau/Aβ42 ratio scores.

These findings are important because they demonstrate that consistent blood-based markers can be identified across independent cohorts and that many blood-based markers are related to CSF markers, consistent with recent findings.[6] Additionally, several of the markers overlapped with the top serum-based markers from a biomarker algorithm that utilized the same assay platform from an independent cohort.[3] Conversely, this study highlights some of the limitations to the field. The fact that 6 markers were significantly, but inversely, associated with MCI/AD status across the Penn and WU cohorts, even though the same assay platform was utilized, is of concern. While the methods across groups were largely consistent, there were differences. For example, fasting samples were collected without EDTA at WU, whereas nonfasting samples were collected at Penn using EDTA tubes. Of greater concern is the fact that only 6 of the 17 markers from the Penn and WU cohorts successfully applied to the ADNI cohort, which again used the same assay platform. As is the case with most large-scale multiplex platforms, the performance of some markers will be very stable across batches (e.g., CRP) whereas others may vary drastically, so batch effects could very well have been involved with this latter finding.

It is likely that the more sophisticated assay and analytical approaches utilized in recent studies will facilitate advancements in many complex diseases, such as AD; however, the step into clinical application is not a simple one. The power of these approaches has clearly been established and additional discovery work is warranted, particularly for targeted

See page 897

From the Department of Internal Medicine, Division of Geriatrics, Institute for Aging & Alzheimer's Disease Research, University of North Texas Health Sciences Center, Fort Worth.

Go to Neurology.org for full disclosures. Disclosures deemed relevant by the author, if any, are provided at the end of this editorial.

populations that have not been included in prior studies (e.g., racial/ethnic minority populations). However, the scientific community also has a responsibility to generate standards and guidelines to facilitate progress in this field as clinical application cannot proceed in their absence without harming both the science and the community. As has been eloquently pointed out previously,[8] the less glamorous aspects of research methodologies need greater attention before many blood-based AD biomarkers can move to clinical application. Such efforts have been ongoing in the neuroimaging and CSF AD biomarker areas for years. Hu and colleagues demonstrate that many plasma markers are consistently related to MCI/AD status across multiple clinic-based cohorts. However, do the markers perform acceptably in nondementia specialty clinic settings? Do the markers validate on different assay platforms? Can the assessment of these markers be improved by tighter consistencies across study methodologies? There are many ongoing efforts to address these and other gaps in the science. A global initiative has formed to begin the process of generating empirically driven standards and guidelines, which includes leaders from the imaging and CSF initiatives. As things currently stand, blood-based markers are not ready for clinical implementation and a great deal of work remains before that can become a possibility. Yet, as demonstrated by the work of Hu et al., great progress is being made.

DISCLOSURE

S. O'Bryant has a patent pending regarding a blood-biomarker screener for Alzheimer disease in conjunction with rules-based medicine. **Go to Neurology.org for full disclosures.**

REFERENCES

1. Ray S, Britschgi M, Herbert C, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. Nat Med 2007;13:1359–1362.
2. Soares HD, Chen Y, Sabbagh M, Rohrer A, Schrijvers E, Breteler M. Identifying early markers of Alzheimer's disease using quantative multiplex proteomic immunoassay panels. Ann NY Acad Sci 2009;1180:56–67.
3. O'Bryant SE, Xiao G, Barber R, et al. A serum protein-based algorithm for the detection of Alzheimer's disease. Arch Neurol 2010;67:1077–1081.
4. Laske C, Leyhe T, Strandsky E, Hoffmann N, Fallgatter A, Dietzch J. Identification of a blood-based biomarker panel for classification of Alzheimer's disease. Int J Neuropsychopharmacol 2011;14:1147–1155.
5. Reedy MM, Wilson R, Wilson J, et al. Identification of candidate IgG biomarkers for Alzheimer's disease via combinatorial library screening. Cell 2011;144:132–142.
6. O'Bryant SE, Xiao G, Barber R, Huebinger R, Wilhelmsen K, Edwards M. A blood-based screening tool for Alzheimer's disease that spans serum and plasma: findings from TARC and ADNI. PLoS One 2011;6:e28092.
7. Hu WT, Holtzman DM, Fagan AM, et al. Plasma multianalyte profiling in mild cognitive impairment and Alzheimer disease. Neurology 2012;79:897–905.
8. Breteler MB. Mapping out biomarkers for Alzheimer's disease. JAMA 2011;305:304–305.